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09/832,069	04/10/2001	Marschall S. Runge	CLFR:183US	8710

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 09/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,069	RUNGE ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,8,9 and 14-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,8,9 and 14-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. This action is in response to the papers filed July 5, 2005. Currently, claims 6, 8-9, 14-23 are pending.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 6, 16-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for measuring the amount of oxidative stress in an individual by detecting the amount of DNA damage per length of DNA using QPCR, does not reasonably provide enablement for detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of

direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method for measuring the amount of oxidative stress in an individual by detecting the amount of DNA damage per length of DNA using QPCR, detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches that tissue ischemia, OXPHOS gene defects, environmental toxins, mtDNA mutations, decreased cellular ATP and oxygen radical formation all affect oxidative phosphorylation dysfunction which leads to tissue degeneration and cell death (Corral-Debrinski et al. 1992). The art does not teach how the amount of mtDNA damage is affected or associated by each of these factors.

Guidance in the Specification.

The specification states "a person having ordinary skill in this art would recognize that measurement of mitochondrial DNA damage is only one potential method to

determine oxidative stress. Any downstream or resultant effect of mitochondrial DNA damage will reflect the same disease process. For example, measurement of mitochondrial protein production, changes in mitochondrial ATP production would accomplish the same goal. The specification provides no evidence teachings regarding the relationship between mtDNA damage and mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. The specification does not teach how these measurements are associated. A mutation in mtDNA may cause such problems with the mtDNA damage that there is no protein production, for example. Thus, measuring protein production of zero due to a truncation mutation would not provide any guidance of the quantity of DNA damage. Since only one mutation may completely negate the protein production, it is unpredictable that this would provide the skilled artisan with the amount of mtDNA damage present. Alternatively, the lesions or mutations/damage may occur in non-coding regions which do not affect protein. The specification has not taught that there is any direct tie. Similarly, the specification does not provide any links between mitochondrial mRNA production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. Reduced ATP could be a single lesion and not due to a larger number of quantitative lesions in the genome. The knockout of mitochondrial enzyme with a single mutation could cause dysfunction.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try.

Working Examples

The specification has no working examples of measuring the *amount* of mtDNA damage in tissue using mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied. As discussed above, there is no guidance or teachings in the specification how measurements of the amount of mtDNA damage in a tissue is associated with mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. There are many other factors which would affect each of theses quantities which may not be related to amount of mtDNA damage. Further, there may be several serious mutations which would dramatically affect mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state which would not allow for quantification of mtDNA damage using mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the specification and the art does not teach how the amount of mtDNA in a tissue may be associated with mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that a copy of the Corral-Debrinski article was not included. This argument has been thoroughly reviewed, but is not found persuasive because the Corral-Debrinski article was cited on an 892 dated February 5, 2004 and a copy was provided at that time. In the event that applicant requires a substitute copy, the examiner will provide a courtesy copy.

The response asserts that the art does teach how the amount of mtDNA damage is affected or associated with each of the factors in question. The response cites to four post filing date articles, namely Ballinger, 2000; Cadenas, 2000; Halmosi, 2001; and Williams, 2000 to support the position that the art teaches how the amount of

mtDNA damage is affected by mt mRNA production, mtprotein production, mt oxidative phosphorylation, mt ATP production and mt redox state. This argument has been thoroughly reviewed, but is not found persuasive because the enablement determination is made given what is known at the time the invention was made. As provided by MPEP 2164.05, "To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention." Here, the specification nor the prior art appear to provide any information regarding detecting mtDNA damage by measuring mitochondrial mRNA production, mitochondrial protein production, mitochondrial oxidative phosphorylation, mitochondrial ATP production or mitochondrial redox state.

The response asserts that the examiner's scientific reasoning is flawed. The response focuses on a particular example, however this example appears to be focused on a large sample. The claim does not require a large sample, but could be limited to a particular cell. Further the response asserts that the claim is drawn to blood. The claim

does not appear to be limited to blood, but be drawn to hematopoietic tissue which would also encompass bone marrow cell, for example. MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the "totally unfounded and contrary to what a scientist would expect" and "that a direct tie between the amount of gene mutational damage and the expression of any given gene, mRNA etc, is, simply put, self evident" should be supported by an affidavit.

The response asserts that no factors which affect the quantities have been provided under the section of quantity of experimentation. This argument has been considered but is not convincing because the particular examples of truncation and non-coding mutations was particular provided by the examiner. Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 8-9, 14-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 6, 8-9, 14-23 are indefinite because it is unclear whether the final clause of the method is directed to detecting amount of damage or mere presence of damage. The claim states, "wherein such damage is indicative of oxidative stress in said individual." Thus, the claim does not particularly appear to require establishing a correlation based upon any amount or ration or other measurement of quantity of damage.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Filser et al. (Biochemical and Biophysical Research Comm. Vol. 233, pages 102-107, 1997).

Filser teaches quantification of wild-type mitochondrial DNA and its 4.8-kb deletion in rat organs. Filser teaches oxidative damage to mtDNA is considered a major contributor in aging. Filser reports a systematic investigation of 10 different tissues and organs of rats was performed. The amount of mtDNA and age-dependent deletion was determined by competitive polymerase chain reaction. MtDNA was detected in all 10

tissues and organs. Filser teaches that the mtDNA4834 in bone-marrow and muscle of a rat was quantified (page 103, col. 2, last para). Figure 2 illustrates the amount of mtDNA and mtDNA 4834 in 10 different organs and tissues. The ration of mtDNA 4834 to wildtype mtDNA was presented for bone marrow, a hematopoeitic tissue. Filser discusses several strategies for quantitative PCR to quantify deletions. Therefore, Filser teaches a method of measuring oxidative stress by measuring the amount of mtDNA damage in hemapoietic tissue.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 6, 7, 8, 9, 14, 15, 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (Circulation, Vol. 96, No. 8, Suppl. P. I605, October 21, 1997) in view of Filser et al. (Biochemical and Biophysical Research Comm. Vol. 233, pages 102-107, 1997).

The instant specification defines "oxidative stress" to refer to pathophysiological effects of reactive oxygen species, such as H2O2, superoxide, peroxynitrate, and other reactive oxygen species (page 25 of the specification).

Yan et al. (herein referred to as Yan) teaches in vivo evidence of the relationship of reactive oxygen species and mitochondrial DNA damage in atherosclerosis.

Specifically, Yan teaches assaying both diseased and normal human aortic tissues for DNA damage using a gene-specific quantitative PCR assay. Yan teaches designing primers to amplify a fragment of the human mitochondrial genome and a nuclear fragment within the beta-globin gene. Fresh surgical specimens of normal and atherosclerotic human aorta were immediately frozen in liquid nitrogen. Yan reports that mtDNA damage detected in atherosclerotic tissue was 2 to 5 fold higher than that of human aortic samples without evidence of atherosclerosis. The evidence suggest that the average DNA lesion frequency in the mitochondrial genome was approximately four times higher than that in the nuclear B-globin gene (limitations of Claim 6, 7, 8). Yan teaches that the levels of H2O2 and O2- were assessed using a peroxidase-H2O2 formation assay. The results of Yan suggest that an increase in H2O2 and O2- levels in patients with CAD compared to those without CAD, consistent with a correlation between mtDNA damage and ROS generation. Yan teaches that the data suggest that oxidative mtDNA damage may play a role in atherosclerotic lesion development.

Yan does not specifically teach using a hematopoeitic tissue.

However, Filser teaches quantification of wild-type mitochondrial DNA and its 4.8-kb deletion in rat organs. Filser teaches oxidative damage to mtDNA is considered a major contributor in aging. Filser reports a systematic investigation of 10 different tissues and organs of rats was performed. The amount of mtDNA and age-dependent deletion was determined by competitive polymerase chain reaction. MtDNA was detected in all 10 tissues and organs. Filser teaches that the mtDNA4834 in bone-marrow and muscle of a rat was quantified (page 103, col. 2, last para). Figure 2

illustrates the amount of mtDNA and mtDNA 4834 in 10 different organs and tissues. The ration of mtDNA 4834 to wildtype mtDNA was presented for bone marrow, a hematopoeitic tissue. Filser discusses several strategies for quantitative PCR to quantify deletions. Therefore, Filser teaches a method of measuring oxidative stress by measuring the amount of mtDNA damage in hemapoietic tissue.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified mitochondrial damage by comparing the amount of damage in patient and control samples using bone marrow, as taught by Filser. Filser teaches a wide range of tissues which would be amenable to analysis including bone marrow. Therefore, the ordinary artisan would have been motivated to have used any of the tissues known to harbor mitochondrial mutations for analysis. Therefore, substituting a bone marrow sample, as taught by Filser, for the aortic tissues sample of Yan would have been obvious to the ordinary artisan at the time the invention was made.

5. Claims 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (Circulation, Vol. 96, No. 8, Suppl. P. I605, October 21, 1997) in view of Filser et al. (Biochemical and Biophysical Research Comm. Vol. 233, pages 102-107, 1997) as applied to Claims 6, 7, 8, 9, 14, 15, 21 above and further in view of VenMurthy et al. (Acta Biochimica Polonica, Vol. 43, No. 1, pages 227-240, 1996).

Neither Yan nor Filser specifically teach using blood samples.

However, VenMurthy teaches studying the vulnerability of the mitochondrial genome to oxidative stress (page 233, col. 1). VenMurthy teaches that because of their high reactivity and short life, the hydroxyl radicals produced in mitochondria would be expected to produce deleterious effects mainly in this organelle (page 234, col. 1). VenMurthy teaches that the spontaneous mutation rate of mtDNA is considerably higher than that of nDNA. VenMurthy teaches that a variety of chronic degenerative diseases that affect the brain, heart, muscle, kidney and endocrine glands have been shown to result from mutations in mtDNA including LHON, MERRF, MELAS, and fatal infantile cardiomyopathy. VenMurthy also teaches that a variety of more common degenerative disorders such as heart disease, adult-onset Alzheimer's disease and aging, may also be related to mtDNA mutations (page 235, col. 1). VenMurthy specifically teaches investigation of mtDNAs isolated from blood lymphocytes from patients. VenMurthy teaches that blood cells represent the most accessible and most readily available of human tissues. VenMurthy teaches that they exist in continuous and intimate contact with the dyslipidemic plasma and their mtDNA would therefore be expected to show any damage resulting from the abnormal environment in their milieu (page 236, col. 1). VenMurthy teaches lymphocytes are selected for their abundance, their mitochondrial content and certain special features of their metabolism. VenMurthy teaches that deletions and insertions in mtDNA was carried out by PCR amplification of consecutive overlapping regions of mtDNA.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified mitochondrial damage by comparing the

amount of damage in patient and control samples using blood, as taught by VenMurthy. While VenMurthy's assays appear to fail to demonstray differences in the mtDNA mutations of positive versus negative control samples, VenMurthy specifically teaches sampling blood cells for mtDNA damage. As pointed out clearly in the response of July 5, 2005, VenMurthy fails to teach a method for quantification of mtDNA mutations. Therefore, the methodology of VenMurthy differs from that of Yan and Filser. Filser analyzes 10 various tissues and organs and detects mtDNA mutations in all the tissues. VenMurthy teaches mtDNA mutations in blood cells. There would have been a reasonable expectation of success, given the quantitative study of Filser, that sampling blood samples taught by VenMurthy would provide results for quantitative analysis. VenMurthy specifically teaches the benefit of using blood samples, such as white blood cells (i.e. lymphocytes). VenMurthy teaches that blood cells represent the most accessible and most readily available of human tissues and that they exist in continuous and intimate contact with the dyslipidemic plasma and their mtDNA would therefore be expected to show any damage resulting from the abnormal environment in their milieu (page 236, col. 1). Therefore, the ordinary artisan would have been motivated to have used the most accessible tissue available which allows for detection of mtDNA damage, i.e. blood/white cells. The ordinary artisan would have been motivated to have substituted blood for the human aorta tissue which was invasively obtained by Yan. A non-invasive procedure for tissue collection would have been an obvious benefit to the method of Yan. Therefore, substituting a blood sample, as taught by VenMurthy, for the

aortic tissues sample of Yan would have been obvious to the ordinary artisan at the time the invention was made.

6. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (Circulation, Vol. 96, No. 8, Suppl. P. I605, October 21, 1997) in view of Filser et al. (Biochemical and Biophysical Research Comm. Vol. 233, pages 102-107, 1997) as applied to Claims 6, 7, 8, 9, 14, 15, 21 above and further in view of Van Houten (US Pat. 5,989,816, November 23, 1999).

Neither Yan, nor VenMurthy specifically teach treating DNA with FAPY glycosylase prior to PCR amplification.

Van Houten however teaches method for detection DNA damage by detecting 8-oxo-deoxyguanosine (8-oxo-G-lesion) using FAPY glycosylase. Van Houten specifically teaches that the assay efficiently detects most forms of base damage and DNA single and double strand breaks. The FAPY converts the 8-oxo-dG strand break with a glycosylase/endonuclease from E. coli. The DNA was used to determine the number of lesions/17.7kb.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the mtDNA damage methods of Yan in view of VenMurthy with the teachings of Van Houten. Van Houten specifically teaches that to directly measure some DNA lesions it is necessary to first convert the 8-oxodG to a strand break with a glycosylase/endonuclease. Therefore the ordinary artisan would have recognized that strand damage methods with 8-oxodG requires treatment with

FAPY to determine the amount of damage. Thus, the ordinary artisan must treat the DNA with FAPY glycosylase prior to PCR amplification for detection of 8-oxo-G lesions.

Conclusion

7. **Claims 6, 8-9, 14-23 are rejected.**

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
September 19, 2005